Disseminated Idiopathic Myofasciitis in Ferrets

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KEYWORDS

• Ferrets • Myofasciitis • Polymyositis • Myositis • Neutrophilia

Disseminated idiopathic myofasciitis (DIM) is a recently identified disease in the domestic ferret, *Mustela putorius furo*.[1,2] The disease was first recognized in late 2003, although the earliest possible case this author (K.D.R.) has identified is from 1999. The most recent case, at the time of this writing, was from January 2010. DIM has also been termed ''polymyositis'' and ''myositis'' and is a severe inflammatory condition that affects primarily muscles and surrounding connective tissues.[1,2] The authors have approximately 100 suspected cases on file with about half having been confirmed via histopathology.

Inflammatory myopathies are a heterogeneous group of autoimmune or immune-mediated diseases that affect muscles[3–6] and have been studied in a number of species, including humans[3,7,8] and dogs.[4,9,10] Four major types of idiopathic inflammatory myopathy in humans include dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (NM).[7,8,11] These myositides appear clinically, histologically, and pathogenically distinct [N]. Canine models for polymyositis and dermatomyositis exist,[9,10,12–15] as does a canine form of immune-mediated masticatory myositis.[4,9,16]

Animal models of inflammatory myopathies have clarified the immunopathogenesis of some of these disorders. Iatragenically induced localized myositis associated with administration of vaccines has been documented in cattle.[17,18] Rats and mice have been used as models for polymyositis, and experimental autoimmune myositis has been induced in rabbits and guinea pigs following immunization of muscle.[19,20] Although research on DIM has been ongoing since it was first described, the etiopathogenesis of this disease in ferrets is still unknown. Advances in the understanding of

The American Ferret Association has established a research fund to study DIM.

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human and animal inflammatory myopathies may help elucidate the pathogenesis of DIM in ferrets.

This article summarizes clinical and pathologic findings in DIM patients. Recommended diagnostic procedures and clinical management are addressed, and possible etiologies for the disease are discussed.

SIGNALMENT AND HISTORY

DIM generally affects ferrets younger than 18 months old. Age range for early cases was 5 months to 24 months of age with an average age of 10 months,[1] and recently cases of ferrets as old as 4 years have been diagnosed. Both male and female ferrets are susceptible to DIM. There does not appear to be an association between susceptibility of the disease and coat color. Ferrets diagnosed with DIM have been mostly from 2 large breeding facilities, but a few were from private breeders. Almost all ferrets had been neutered and descented at their original breeding facility before shipment. Most ferrets suspected or confirmed to have DIM lived in multiferret households, and some were residing at shelters or rescue facilities. Households were in a number of states throughout the United States. Ferrets diagnosed with DIM have been fed various diets, including ones mostly formulated for ferrets, but also some cat and kitten products.

Vaccine histories were evaluated from cases if the information was available. A number of ferrets received the recommended series of distemper vaccinations. Many ferrets were inoculated with only one canine distemper vaccination, between 4 and 7 weeks of age, at the breeding facility. Some ferret owners have the misconception that young ferrets have been fully vaccinated against canine distemper before being shipped to the pet store.

Early case histories indicated that all confirmed DIM cases had been vaccinated with one particular distemper vaccine, Fervac-D (United Vaccines, Madison, WI, USA), which is no longer being produced. Two other distemper vaccines given to ferrets diagnosed with DIM were Purevax (Merial, Athens, GA, USA) and Galaxy-D (Schering-Plough Animal Health, Omaha, NE, USA). Some DIM ferrets received an approved rabies vaccine (Imrab-3, Merial).

Because Fervac-D is no longer available, large ferret breeding facilities have had to choose an alternative product to vaccinate and protect young ferrets from canine distemper. Recent inquiries to 3 large ferret breeding facilities revealed that Distox-Plus (a modified live mink distemper-virus enteritis vaccine, *Clostridium botulinum* type-C-*Pseudomonas aeruginosa* bacterin-toxin) (Schering-Plough Animal Health) is currently being used and is cost effective. Distem-R TC (a modified live mink distemper vaccine) (Schering-Plough Animal Health) was being used in some facilities after Fervac-D was removed from the market, but now it too is no longer available. Although Purevax is the only distemper vaccine currently approved for use in ferrets, many practitioners and shelters use Galaxy-D.

CLINICAL SIGNS

The onset of clinical signs for DIM is usually acute to subacute, often followed by rapid decline over a period of 12 to 36 hours. Clinical signs for DIM are summarized in **Table 1**. Afflicted ferrets usually have multiple, concurrent symptoms. The most common initial clinical signs are a high fever (often 104–108°F), severe lethargy, paresis, and dehydration (**Fig. 1**). Most affected ferrets are depressed but cognizant. Other symptoms observed during the onset of DIM include inappetence, enlarged lymph nodes, subcutaneous masses, and abnormal stools. Greenish, mucoid, and

Table 1
Clinical signs of ferrets with DIM

Most Common Signs	Somewhat Common Signs	Less Common Signs
Fever	Painful (mostly lumbosacral/rear legs)	Serous nasal discharge
Lethargy	Abnormal stools	Pinpoint dermal lesions (often orangish)
Paresis	Enlarged lymph nodes	Ocular discharge
Depression	Subcutaneous masses	Labored/congested breathing; coughing
Inappetence	Weight loss	Panting
Dehydration	Tachycardia	Bruxism
	Tachypnea	Pale gums
	Heart murmur	Edema
		Seizures

dark diarrhea has been observed in several patients. Some ferrets will refuse crunchy food but will eat soft food. A number of suspected and confirmed patients with DIM have developed hyperesthesia or dysesthesia, displaying responses indicative of pain when they are palpated or touched. The greatest sensitivity is usually in the lumbosacral region or hind legs. Tachycardia (heart rate often over 300 beats per minute), tachypnea, and heart murmurs occur somewhat often and seem to become more prominent as the disease progresses.

Other signs that may be observed in ferrets with DIM include serous nasal discharge, ocular discharge, bruxism, pale gums, panting, labored or congested

Fig 1. Ferrets with DIM are typically depressed, very lethargic, paretic, and dehydrated. (*Courtesy of* Yvonne DeCarlo; with permission.)

breathing, coughing, and rarely edema or seizures. Some ferrets have had skin lesions such as infected hair follicles, small dermal masses, or pinpoint orangish dots on the trunk or face. Although clinical signs of DIM usually develop quickly, the duration of the illness can be days to weeks, or even months. Most ferrets with DIM have continued to progressively decline until they either died or were humanely euthanized.

DIAGNOSTIC RESULTS

Hematology

Although the white blood cell (WBC) count may initially be in the normal range, most ferrets with DIM eventually exhibit a moderate to marked mature neutrophilia, occasionally with a left shift. The WBC count is less than 50,000/μL in most DIM cases (normal reference range for WBCs in ferrets is 2500–8000/μL; Antech Diagnostics), but the mature neutrophil count has approached 100,000/μL in a few cases. Neutrophils are often slightly to moderately toxic in patients with DIM. Mild to moderate anemia is a common finding in ferrets with DIM. The anemia may be initially nonregenerative and then later become regenerative. Target cells, schistocytes, and Dohle bodies have been identified rarely in patients with DIM.

Serum chemistry values in ferrets with DIM often reveal mild hyperglycemia and hypoalbuminemia. Serum alanine aminotransferase (ALT) has also been mildly to moderately increased in several patients with DIM. Interestingly, creatine kinase (CK), a value typically elevated with severe inflammation and muscle tissue necrosis, is not elevated in ferrets with DIM. As discussed later, this is attributed to the fact that although there is severe inflammation within the muscle bundles and fascil planes between muscles, there is usually minimal muscle necrosis. Ferrets that underwent additional diagnostic testing were negative for canine distemper, Aleutian disease virus, feline infectious peritonitis, *Sarcocystis,* and *Bartonella*.

Additional Diagnostic Procedures

Radiologic and ultrasonographic findings in patients with DIM often reveal an enlarged spleen and/or abdominal lymph nodes, but these nonspecific findings are otherwise not contributory to the diagnosis. Exploratory surgery does not reveal pertinent gross lesions in the abdominal viscera other than splenomegaly or lymphadenomegaly. Aerobic and anaerobic bacterial cultures from various affected tissues have been negative and have not revealed a bacterial etiology for DIM. Urinalysis results from several cases included a slightly elevated pH of approximately 7 to 8 (normal range is 5.5–6.5)[21] and the presence of struvite or amorphous phosphate crystals.

PATHOLOGIC FINDINGS

The gross, histologic, and electron microscopic findings that characterize DIM have been described.[1] Gross and histologic images are illustrated in **Figs. 2–10**. Gross lesions from deceased ferrets with DIM may be inapparent or subtle in acutely affected ferrets, or quite striking in more chronic cases. Gross lesions that may be seen include red and white mottling of the esophagus; white streaks in the diaphragm, lumbar, and leg muscles; and marked atrophy of diaphragm and skeletal muscle in advanced cases.[1] Lymphadenomegaly and splenomegaly are also observed frequently.[1] Histologically, all skeletal muscle as well as heart muscle can be affected. Microscopic lesions typically are multifocal and include mild to severe suppurative to pyogranulomatous inflammation in the fascia between muscle bundles, extending into the perimysium and endomysium, and rarely causing necrosis of muscle fibers. Inflammation often extends into surrounding adipose tissue, and muscle atrophy and fibrosis may

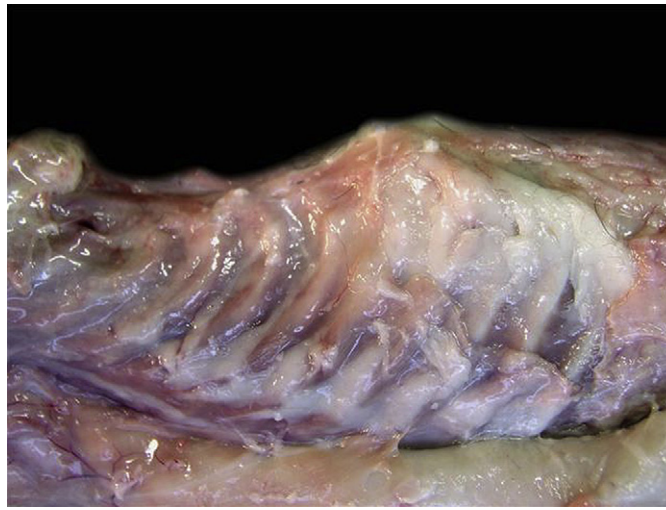

Fig. 2. Ferret, myofasciitis. Note rib cage has adequate fat stores but atrophy of intercostal muscles.

be apparent in ferrets with chronic disease. The circumferential transmural nature of the infiltrate in the muscular tunics along the entire length of the esophagus in advanced cases is possibly a pathognomonic lesion. Electron microscopic examination of the muscle reveals mitochondrial swelling, edema between myofibrils, and myofibril and Z-band disruption. No ultrastructural abnormalities are noted in leukocytes adjacent to affected muscle. All muscle groups appear to be involved in the inflammatory process, and it is likely that the clinical signs observed in patients with DIM are a result of the pain and atrophy that accompany this condition. Nonmuscular organs such as fat, brain, liver, lung, trachea, spleen, and bone marrow may also have mild neutrophilic inflammation in affected ferrets.[1] Extramedullary hematopoiesis is commonly found in the spleen and bone marrow and myeloid left shift without congestion is prominent, which distinguishes the splenic lesion from the mixed extramedullary hematopoiesis and congestion more commonly associated with splenomegaly in old ferrets. Bronchopneumonia is sometimes observed, presumably caused by aspiration associated with force feeding or regurgitation because of the esophageal lesions.

TREATMENT

One consistent characteristic of ferrets with DIM has been a general lack of response to treatment and a high mortality rate. For 3 years after DIM was first recognized, treatment with an array of antibiotics and various medications (glucocorticoids, nonsteroidal anti-inflammatory drugs, antipyretics, analgesics, interferon, and cyclosporine), along with supportive care was ultimately unsuccessful in all patients. One patient received a dose of cyclophosphamide the day before the owners elected euthanasia. Some patients seemed to temporarily respond to treatment with the immune-modulating drugs, but the patients later relapsed and succumbed to the disease. Acupuncture was used as a form of therapy in one confirmed case and one suspected case. Both owners felt that acupuncture was advantageous to their ferrets by providing temporary, palliative relief (**Fig. 11**A and B).

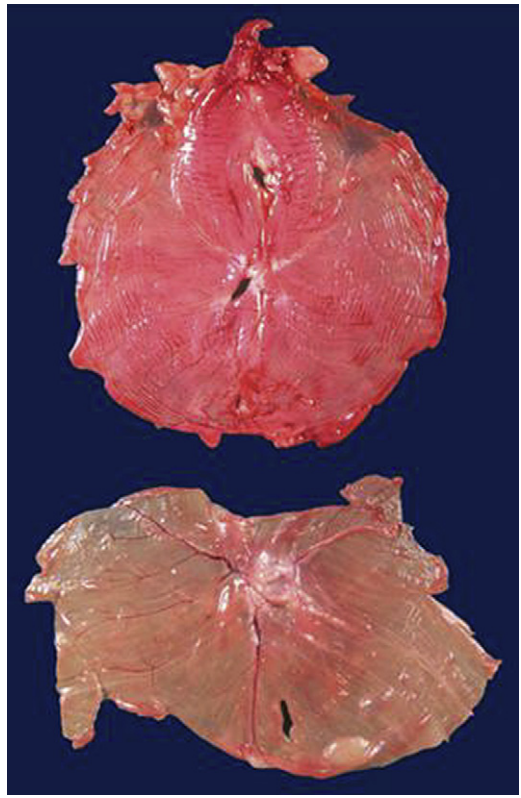

Fig 3. Ferret, myofasciitis. Note normal diaphragm of aged-matched control ferret (*top*), and atrophic muscles of affected diaphragm (*bottom*). (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

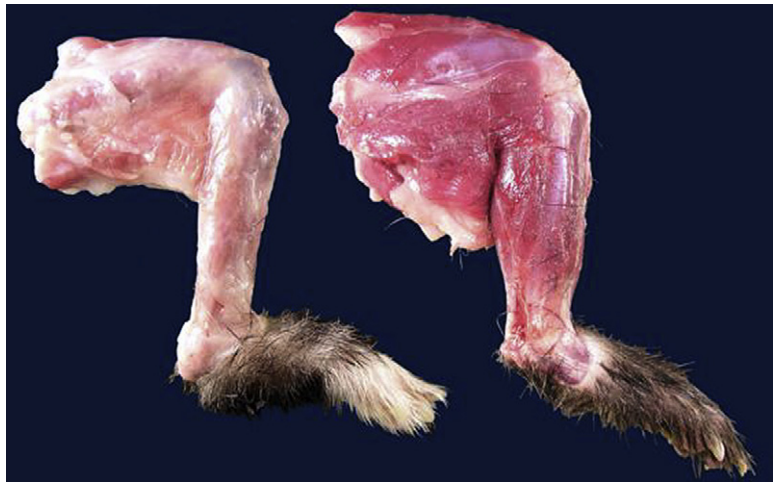

Fig. 4. Ferret, myofasciitis. Note normal hind leg of age-matched control ferret (*right*), and atrophic muscle of affected ferret (*left*). (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

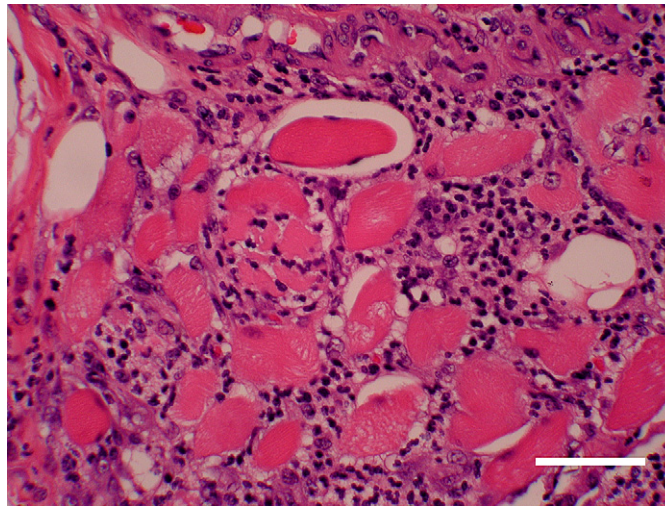

Fig. 5. Ferret, myofasciitis. Biceps femoris. Note infiltrate of neutrophils within and around myofibers, associated with myofiber displacement and necrosis (hematoxylin and eosin [H&E] stain, bar = 80 μm).

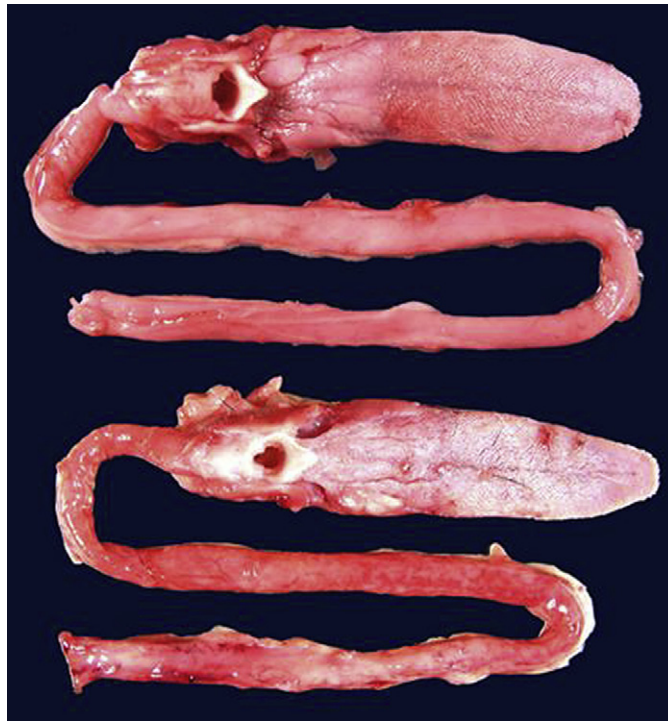

Fig. 6. Ferret, myofasciitis. Note dorsal-ventral flaccid appearance of normal esophagus (*top*) and turgid round red-white mottled appearance of affected esophagus (*bottom*). Also note atrophy of tongue and hyperkeratosis (due to secondary candidiasis) in affected ferret. (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

Fig. 7. Ferret, myofasciitis. Transverse section through esophagus. Note transmural circumferential inflammatory cell infiltrate that spares only the mucosa (H&E stain, bar = 270 μm). (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

Since the beginning of 2006, a few confirmed cases and several suspected cases have improved and are doing very well after receiving a combination of drugs including cyclophosphamide, prednisolone, and chloramphenicol. The recommended treatment protocol for ferrets with DIM is summarized in **Table 2**. Prednisolone and chloramphenicol without the cyclophosphamide has not resulted in recovery or even significant improvement of ferrets with DIM. Cyclophosphamide, a nitrogen-mustard derivative and chemotherapeutic agent with alkylating metabolites, has marked immunosuppressive activity and causes reduction in WBC and antibody production.[22]

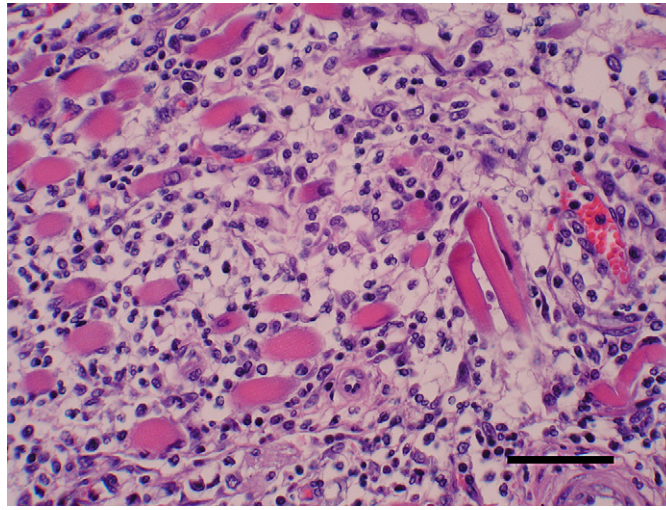

Fig. 8. Ferret, myofasciitis. Muscular tunic of esophagus. Note myofiber disarray owing to infiltrate of large numbers of neutrophils (H&E stain, bar = 160 μm). (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

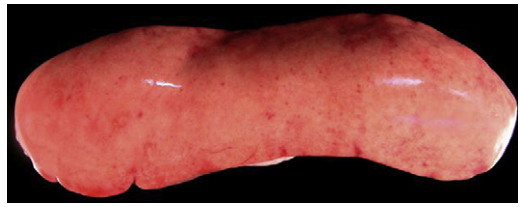

Fig. 9. Ferret, myofasciitis. Note generalized pallor of enlarged spleen. (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

In veterinary medicine, it is used both as an antineoplastic agent and as an immunosuppressant.[22] If DIM is an immune-mediated disease, cyclophosphamide is most likely reversing or suppressing the deleterious effects of DIM via immunosuppression, but the mechanism of action of this drug in this particular disease has not been discerned. Interestingly, treatment for the human myopathies polymyositis and dermatomyositis include primarily glucocorticoids and secondarily glucocorticoid-sparing agents such as azathioprine and methotrexate, but inclusion body myositis is generally refractory to immunosuppressive therapy and intravenous gamma globulins.[23,24]

Three biopsy-confirmed DIM cases recovered after being treated with the recommended treatment protocol. One ferret died 3.5 years after onset of DIM from other causes. Two ferrets are still living at the time of this writing, approximately 3.5 years after onset of the disease. Several suspected cases appear to have recovered after receiving presumptive treatment with the DIM treatment protocol, but they were not biopsy-confirmed cases. One confirmed case began treatment for DIM 6 days after onset of signs, improved significantly over a period of a week, then relapsed and was euthanized.

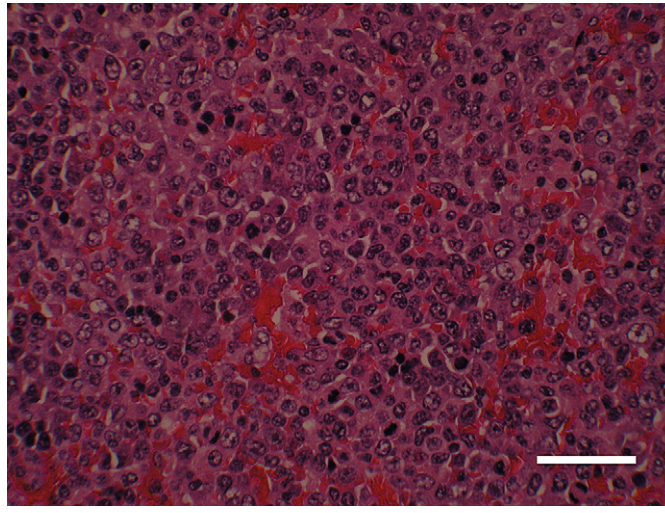

Fig. 10. Ferret, myofasciitis. Note myeloid hyperplasia in red pulp of spleen, which accounts for the splenomegaly and grossly pale appearance of the spleen (H&E stain, bar = 150 μm). (*From* Garner MM, Ramsell K, Schoemaker NJ, et al. Myofasciitis in the domestic ferret. Vet Pathol 2007;44(1):25–38; with permission.)

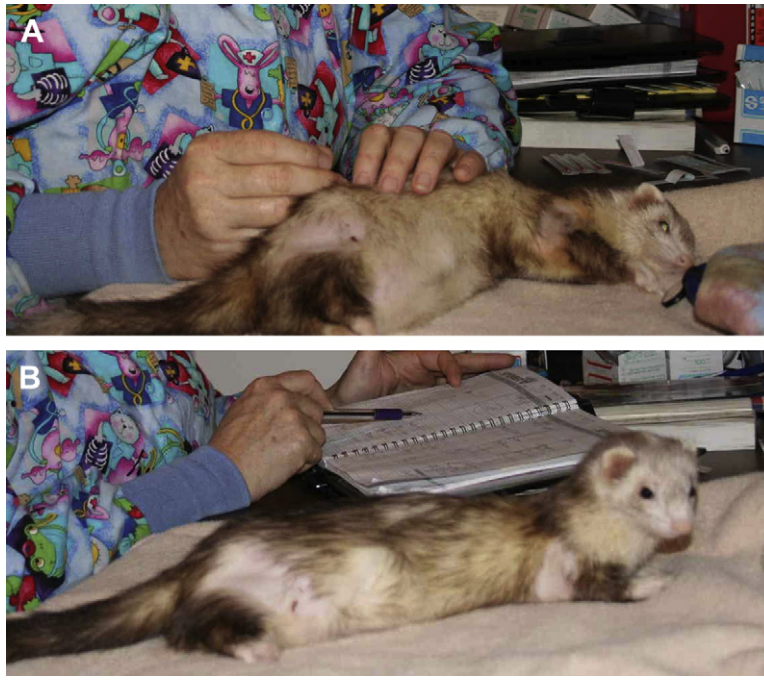

Fig. 11. A DIM-confirmed ferret before and after acupuncture treatment. The ferret is depressed and recumbent at the beginning of the session (*A*). The ferret is more alert and upright at the end of the session (*B*). (*Courtesy of* Nancy Wilson; with permission.)

Table 2
Recommended DIM treatment protocol

Drug	Suggested Dose	Potential Side Effects
Prednisolone[a]	1 mg/kg PO q 12 h for 3 months, then q 24 h until recovery has been achieved (wean off)	GI ulceration Muscle wasting Elevated liver enzymes Abdominal fat deposition Dermatologic effects PU/PD/polyphagia
Cyclophosphamide[b]	10 mg/kg on day 1, day 14, then every 4 weeks for 3 months or until recovery has been achieved	Neutropenia Hemorrhagic cystitis GI toxicity
Chloramphenicol[c] (palmitate)	50 mg/kg PO q 12 h for 6–8 weeks	Bone marrow suppression GI signs

Abbreviations: GI, gastrointestinal; PD, polydipsia; PO, oral; PU, polyuria; q, every.

[a] Prednisolone can be made up as a "bitter-free" suspension that is more palatable than some human commercial formulations.

[b] Subcutaneous fluids should be administered in conjunction with administration of cyclophosphamide to help reduce potential occurrence of hemorrhagic cystitis. Cyclophosphamide can be given via a subcutaneous injection. Oral cyclophosphamide is not palatable to ferrets, and partial tablets should not be given as the drug is not evenly distributed throughout the tablet. A complete blood count should be done before each cyclophosphamide treatment.

[c] Chloramphenicol palmitate oral suspension can be made at a compounding pharmacy.

POTENTIAL ETIOLOGIES

Although bacterial infection was considered initially as a possible etiology for DIM based on the suppurative nature of the lesions, the failure of patients with DIM to respond to a variety of antibacterial drugs and the inability to demonstrate bacteria in the lesions has prompted investigation into other possibilities. Viral infections usually do not evoke such a severe suppurative inflammatory response as that observed with DIM, and no viral agents have been detected to date by electron microscopy. With the recent advent of crystal array molecular testing for the presence of virus nucleic acid in tissue, a viral etiology may be further explored. Protozoa have not been identified histologically in DIM lesions, and immunohistochemical stains have been negative for *Sarcocystis neurona*, *Neospora caninum*, and *Toxoplasma gondii*. Fungal stains and cultures have also been negative, making a fungal infection also unlikely. Affected ferrets have been fed a variety of diets and there is no known exposure to any toxic substances, so food contaminants or environmental toxins are unlikely causes of DIM.

It is noteworthy that a disease histologically indistinguishable in lesion morphology and distribution was inadvertently induced in ferrets during an experimental vaccine trial.[1] The only known commonality among ferrets suspected or confirmed to have DIM is the administration of at least 1 dose of canine distemper vaccine. Vaccines and vaccine aduvants are being investigated as a potential cause for this condition. Adjuvants can cause local tissue reactions, granulomas, or abscesses at injection sites in other species.[25] Polyarthritis, uveitis, myositis, and autoimmune reactions have been documented in vaccinated people.[25–27] Animal vaccines, unlike those produced for humans, are often produced in cell lines of the species for which the vaccine is intended, which makes contamination with potentially pathogenic, latent, or passenger viruses more likely.[25]

Since an apparent peak in suspected and confirmed cases during 2004 to 2005, the number of reported DIM cases has decreased quite dramatically over the past 3 years. Age of onset in ferrets with DIM has ranged from 11 weeks to 4 years. One ferret showed signs 1 day after being vaccinated, and another ferret, which had received only the 1 vaccination routinely given at the breeding facility, showed signs 4 years later. If DIM is vaccine-associated, it is difficult to explain why there is such a variable time interval between administration of the canine distemper vaccine and the onset of clinical signs. There may be a delayed mechanism in the development of the disease, or the disease may exist subclinically for a period of time and then progress rapidly after initial clinical signs develop. It is also not understood why some ferrets decline rapidly over a period of only a few days but others seem to remain in a relatively unchanging poor state of health for weeks or even months with supportive care.

Although ferrets have come from different breeders, it is possible there is a genetic predisposition for DIM. There are reports of a heritable predisposition for some forms of myositis in humans[28] and dogs.[15] A syndrome in closely related Akita dogs has many similarities to DIM and appears to have a genetic link.[29] In addition, vaccines, infections, certain drugs, and other factors are known to serve as triggers in development or exacerbation of autoimmune disease in genetically susceptible humans.[30] Interestingly, one ferret (half European polecat and half New Zealand ferret) that came from a private breeder died from DIM, and his father and half brother died at a young age from an illness with signs very similar to DIM. Although we have the vaccine history for the confirmed case, vaccine histories were incomplete for the related ferrets. Genetic predisposition may serve as an explanation as to why DIM in ferrets is uncommon and has such an apparently idiosyncratic response.

Disseminated idiopathic myofasciitis may be an acquired immune-mediated disease, although such diseases generally are not suppurative in nature. In humans, idiopathic inflammatory myopathies are systemic autoimmune diseases that have predominate mononuclear inflammatory cell infiltrates in the skeletal muscle.[6] Cells typically involved in the pathogenesis of disease are B-lymphocytes, T-lymphocytes, macrophages, dendritic cells, and natural killer cells.[6] References to neutrophilic myositis in humans are uncommon, with 2 case reports associating the disease to inflammatory bowel disease[31] and celiac disease.[32] Interestingly, DIM is a type of neutrophilic myositis, and inflammatory bowel disease is common in ferrets.[33]

A variety of molecular alterations occur in inflammatory myopathies of humans. Recent studies reveal that cytokines and chemokines are critically involved in the initiation and progression of the human inflammatory myopathies.[34] DM is mainly a humoral event, whereas PM and IBM are characterized by invasion of autoaggressive cytotoxic T cells and macrophages into viable muscle fibers.[3] Although a general increase of specific chemokines occurs in all 3 inflammatory myopathies, chemokine distribution reflects the 2 different immune responses in these diseases.[3] Interleukin-21, a cytokine produced predominately by CD4+ T cells, has been reported to play an important role in tissue-damaging immune response in various organs, and neutralization of IL-21 appears to have beneficial effects of the progression of inflammatory diseases in mice.[35] Myositis-specific antibodies have been detected in humans with PM and DM and are considered useful markers for clinical diagnosis, classification, and predicting prognosis of these inflammatory myopathies.[23,36] Overexpression of the MHC class I heavy chain protein is a common feature in muscle lesions, including idiopathic myositis, and can lead to severe myositis with rapid onset of muscle weakness and pathologic change in young mice.[37] The MHC/CD8 complex is considered a specific immunopathological marker, as it distinguishes antigen-driven inflammatory cells of PM and IBM from nonspecific, secondary inflammation in other disorders such as dytrophies.[38] These are all examples of how research is progressively clarifying the biochemical pathways and processes of inflammatory myopathies. Advances in molecular immunopathology are elucidating the disease processes in human and animal myopathies and the therapeutic strategies that will be most effective in treating individual patients. Hopefully, information from other studies will guide investigations into the etiology and pathogenesis of DIM.

RECOMMENDATIONS

Ferrets suspected of having DIM should have a thorough physical examination and diagnostic tests, including a comprehensive blood panel, urinalysis, and radiographs. When signalment and clinical signs are consistent with those of DIM and a prominent neutrophilic leukocytosis is present, biopsies of skeletal muscles and any masses or enlarged lymph nodes should be surgically obtained. As DIM has a multifocal distribution, 2 to 3 external skeletal muscle biopsies are recommended from lumbar, hind leg, shoulder, or temporal regions. Animals presenting for necropsy should have a comprehensive tissue set collected for histologic examination, including the target tissues of esophagus, skeletal muscle, and heart. Paired tissue samples should be frozen for future reference.

Ferrets suspected of having DIM should receive aggressive supportive care, including supplemental feedings, fluids, and broad-spectrum antibiotics until a definitive diagnosis can be made. If a ferret is definitively diagnosed with DIM, treatment with cyclophosphamide, prednisolone, and chloramphenicol may be effective. The complete blood count should be monitored regularly in ferrets treated for DIM. Biopsy

and necropsy samples should be submitted for histologic examination for diagnostic purposes and to facilitate DIM research. The American Ferret Association (www.ferret.org) has a DIM case report form that can be completed for presumptive and confirmed cases. Increased awareness of DIM and submission of accurate case reports with complete histories will contribute to our database and contribute to our investigation of this devastating disease in ferrets.

SUMMARY

DIM in ferrets is a severe inflammatory disease that primarily affects skeletal, smooth, and cardiac muscles and surrounding connective tissues. It affects male and female ferrets and is most common in ferrets younger than 18 months old. Although the disease has distinct clinical features, biopsy of skeletal muscle is the only way to get a definitive antemortem diagnosis. DIM has a high mortality rate, but the current treatment protocol has been effective in some cases. Future studies of DIM in ferrets should include continued investigation of potential infectious and vaccine-induced etiologies as well as identifying molecular pathways in the immune system and muscle lesions.

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